



What is claimed is:

A polypeptide chain useful as a subunit of a 1. dimeric osteogenic protein comprising a pair of disulfide-bonded polypeptide chains,

said polypeptide chain having an amino acid sequence sufficiently duplicative of Sequence ID No. 1 or Sequence ID No. 3 such that the dimeric osteogenic protein comprising said polypeptide chain has a conformation capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix.

The polypeptide chain of claim 1 wherein the sequence comprises (Sequence II No. 1):

| Ala 1 | Ala | Arg | Pro | Leu 5 | Lys | Arg | Arg | Gln |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Pro 10 | Lys | Lys | Thr | Asn | Glu 15 | Leu | Pro | His |
| Pro | Asn 20 | Lys | Leu | Pro | Gly | 17e 25 | Phe | Asp |
| Asp | Gly | His 30 | Gly | Ser | Arg | €7Å | Arg 35 | Glu |
| Val | Cys | Arg | Arg 40 | His | Glu | I∘eu | Tyr | Val 45 |
| Arg | Phe | Arg | Asp | Leu 50 | Gly | Trp | Leu | Asp |
| Trp 55 | Val | Ile | Ala | Pro | Gln 60 | Gly | Tyr | Ser |



| - 75- |
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| Ala | Tyr 65 | Tyr | Cys | Glu | Gly | Glu 70 | Cys | Ala |
|------------|------------|------------|------------|-----------|------------|------------|------------|------------|
| Phe | Pro | Leu 75 | Asp | Ser | Cys | Met | Asn 80 | Ala |
| Thr | Asn | His | Ala 85 | Ile | Leu | Gln | Ser | Leu 90 |
| Val | His | Leu | Met | Lys 95 | Pro | Asp | Val | Val |
| Pro 100 | Lys | Ala | Cys | Cys | Ala 105 | Pro | Thr | Lys |
| Leu | Ser 110 | Ala | Thr | Ser | Val | Leu 115 | Tyr | Tyr |
| Asp | Ser | Ser 120 | Asn | Asn | Val | Ile | Leu 125 | Arg |
| Lys | His | Arg | Asn 130 | Met | Val | Val | Lys | Ala 135 |
| Cys | Gly | Cys | His. | | | | | |

The polypeptide chain of claim 1 wherein the sequence comprises (Sequence ID No. 3):

hOP-2

| Ala 1 | Val | Arg | Pro | Leu 5 | Arg | Arg | Arg | Gln |
|-----------|-----------|-----------|-----------|----------|-----------|-----------|-----------|-----------|
| Pro 10 | Lys | Lys | Ser | Asn | Glu 15 | Leu | Pro | Gln |
| Ala | Asn 20 | Arg | Leu | Pro | Gly | 11e 25 | Phe | Asp |
| Asp | Val | Asn 30 | Gly | Ser | His | Gly | Arg 35 | Gln |
| Val | Cys | Arg | Arg 40 | His | Glu | Leu | Tyr | Val 45 |







| Ser | Phe | Gln | Asp | Leu 50 | Gly | Trp | Leu | Asp |
|------------|------------|------------|------------|-----------|------------|------------|------------|------------|
| Trp 55 | Val | Ile | Ala | Pro | Gln 60 | Gly | Tyr | Ser |
| Ala | Tyr 65 | Tyr | Cys | Glu | Gly | Glu 70 | Cys | Ser |
| Phe | Pro | Leu 75 | Asp | Ser | Cys | Met | Asn 80 | Ala |
| Thr | Asn | His | Ala 85 | Ile | Leu | Gln | Ser | Leu 90 |
| Val | His | Leu | Met | Lys 95 | Pro | Asn | Ala | Val |
| Pro 100 | Lys | Ala | Cys | Cys | Ala 105 | Pro | Thr | Lys |
| Leu | Ser 110 | Ala | Thr | Ser | Val | Leu 115 | Tyr | Tyr |
| Asp | Ser | Ser 120 | Asn | Asn | Val | lle | Leu 125 | Arg |
| Lys | Ala | Arg | Asn 130 | Met | Val | Val | Lys | Ala 135 |
| Cys | Gly | Cys | His. | | | | | |

4. The polypeptide chain of claim 1 wherein the sequence comprises (Sequence ID No. 7):

Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa 1

Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa 25

Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa 35



and wherein each Xaa independently represents one of the 20 naturally occurring L-isomer, α -amino acids, and together with said 8 cysteine residues define said polypeptide chain.

5. The polypeptide chain of claim 1 wherein the sequence comprises (Sequence ID No. 8):

Xaa Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys Cys Xaa Xaa Xaa Xaa



70 75

80 85

Xaa Xaa Xaa Xaa Cys Xaa Cys Xaa 90 95

wherein each Xaa independently represents one of the 20 naturally occurring L-isomer, α -amino acids, and together with said 7 cysteine residues define said polypeptide chain.

6. A polypeptide chain useful as a subunit of a dimeric osteogenic protein, said protein being capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix;

said polypeptide chain comprising the amino acid sequence (Sequence ID No. 5):

> Cys Xaa, Xaa, His Glu Leu Tyr Val Xaa, Phe 1

> Xaa₄ Asp Leu Gly Trp Xaa₅ Asp Trp Xaa₆ Ile

Ala Pro Xaa, Gly Tyr Xaa, Ala Tyr Tyr Cys

Glu Gly Cys Xaa, Phe Pro Leu Xaa, Ser Xaa,

Met Asn Ala Thr Asn His Ala Ile Xaa₁₂ Thr

Leu Xaa₁₃ Xaa₁₄ Xaa₁₅ Xaa₁₆ Xaa₁₇ Xaa₁₈ Val

Pro Lys Xaa₁₉ Cys Cys Ala Pro Thr Xaa₂₀ Leu 60 65



Xaa21 Ala Xaa22 Ser Val Leu Tyr Xaa23 Asp

Xaa24 Ser Xaa25 Asn Val Xaa26 Leu Xaa27 Lys

Xaa28 Pro Asn Met Val Val Xaa29 Ala Cys Gly 90 95

Cys His,

wherein Xaa₁ = (Lys or Arg); Xaa₂ = (Lys or Arg); $Xaa_3 = (Ser \ or \ Arg); Xaa_4 = (Arg \ or \ Gln); Xaa_5 = (Gln$ or Leu); Xaa₆ = (Ile or Val); Xaa₇ = (Glu or Gln); $Xaa_8 = (Ala \text{ or Ser}); Xaa_9 = (Ala \text{ or Ser}); Xaa_{10} =$ (Asn or Asp); $Xaa_{11} = (Tyr or Cys)$; $Xaa_{12} = (Val or Cys)$ Leu); $Xaa_{13} = (His or Asn); Xaa_{14} = (Phe or Leu);$ $Xaa_{15} = (Ile or Met); Xaa_{16} = (Asn or Lys); Xaa_{17} =$ (Glu, Asp or Asn); Xaa₁₈ = (Thr, Ala or Val); Xaa₁₉ = (Pro or Ala); $Xaa_{20} = (Gln \ or \ Lys)$; $Xaa_{21} = (Asn \ or \ Lys)$ Ser); $Xaa_{22} = (Ile or Thr); Xaa_{23} = (Phe or Tyr);$ $Xaa_{24} = (Asp, Glu or Ser); Xaa_{25} = (Ser or Asn); Xaa_{26}$ = (Ile or Asp); Xaa_{27} = (Lys or Arg); Xaa_{28} = (Tyr, Ala or His); and $Xaa_{29} = (Arg or Lys)$.

- 7. The polypeptide chain of claim 6 wherein $Xaa_{11} = Cys.$
- A polypeptide chain useful as a subunit of a dimeric osteogenic protein, said protein being capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix;

the amino acid sequence of said polypeptide chain being at least 70% homologous with the amino acid sequence (Sequence ID No. 1):

| Ala 1 | Ala | Arg | Pro | Leu 5 | Lys | Arg | Arg | Gln |
|------------|------------|------------|------------|-----------|------------|------------|------------|------------|
| Pro 10 | Lys | Lys | Thr | Asn | Glu 15 | Leu | Pro | His |
| Pro | Asn 20 | Lys | Leu | Pro | Gly | 11e 25 | Phe | Asp |
| Asp | Gly | His 30 | Gly | Ser | Arg | Gly | Arg 35 | Glu |
| Val | Cys | Arg | Arg 40 | His | Glu | Leu | Tyr | Val 45 |
| Arg | Phe | Arg | Asp | Leu 50 | Gly | Trp | Leu | Asp |
| Trp 55 | Val | Ile | Ala | Pro | Gln 60 | Gly | Tyr | Ser |
| Ala | Tyr 65 | Tyr | Cys | Glu | Gly | Glu 70 | Cys | Ala |
| Phe | Pro | Leu 75 | Asp | Ser | Cys | Met | Asn 80 | Ala |
| Thr | Asn | His | Ala 85 | Ile | Leu | Gln | Ser | Leu 90 |
| Val | His | Leu | Met | Lys 95 | Pro | Asp | Val | Val |
| Pro 100 | Lys | Ala | Cys | Cys | Ala 105 | Pro | Thr | Lys |
| Leu | Ser 110 | Ala | Thr | Ser | Val | Leu 115 | Tyr | Tyr |
| Asp | Ser | Ser 120 | Asn | Asn | Val | Ile | Leu 125 | Arg |
| Lys | His | Arg | Asn 130 | Met | Val | Val | Lys | Ala 135 |
| Cys | Gly | Cys | His. | | | | | |



9. The polypeptide chain of claim 8 wherein the amino acid sequence is at least 80% homologous with the amino acid sequence (Sequence ID No. 1):

| Ala 1 | Ala | Arg | Pro | Leu 5 | Lys | Azg | Arg | Gln |
|------------|------------|------------|-----------|-----------|------------|------------|------------|-----------|
| Pro 10 | Lys | Lys | Thr | Asn | Glu 15 | Leu . | Pro | His |
| Pro | Asn 20 | Lys | Leu | Pro | Gly | 11e 25 | Phe | Asp |
| Asp | Gly | His 30 | Gly | Ser | Arg | Gly | Arg 35 | Glu |
| Val | Cys | Arg | Arg 40 | His | Glu | Leu | Tyr | Val 45 |
| Arg | Phe | Arg | Asp | Leu 50 | Gly | Trp | Leu | Asp |
| Trp 55 | Val | Ile | Ala | Pro | Gln 60 | Gly | Tyr | Ser |
| Ala | Tyr 65 | Tyr | Cys | Glu | Gly | Glu 70 | Cys | Ala |
| Phe | Pro | Leu 75 | Asp | Ser | Cys | Met | Asn 80 | Ala |
| Thr | Asn | His | Ala 85 | Ile | Leu | Gln | Ser | Leu 90 |
| Val | His | Leu | Met | Lys 95 | Pro | Asp | Val | Val |
| Pro 100 | Lys | Ala | Cys | Cys | Ala 105 | Pro | Thr | Lys |
| Leu | Ser 110 | Ala | Thr | Ser | Val | Leu 115 | Tyr | Tyr |
| Asp | Ser | Ser 120 | Asn | Asn | Val | Ile | Leu 125 | Arg |



Lys His Arg Asn Met Val Val Lys Ala 130 135 Cys Gly Cys His.

10. The polypeptide chain of claim 8 wherein the amino acid sequence comprises (Sequence ID No. 1):

| Ala 1 | Ala | Arg | Pro | Leu 5 | Lys | Arg | Arg | Gln |
|------------|-----------|-----------|-----------|-----------|------------|-----------|-----------|-----------|
| Pro 10 | Lys | Lys | Thr | Asn | Glu 15 | Leu | Pro | His |
| Pro | Asn 20 | Lys | Leu | Pro | Gly | Ile ?5 | Phe | Asp |
| Asp | Gly | His 30 | Gly | Ser | Arg | Gly | Arg 35 | Glu |
| Val | Cys | Arg | Arg 40 | His | Glu | Leu | Tyr | Val 45 |
| Arg | Phe | Arg | Asp | Leu 50 | Gly | Trp | Leu | Asp |
| Trp 55 | Val | Ile | Ala | Pro | Gln 60 | Gïy | Tyr | Ser |
| Ala | Tyr 65 | Tyr | Cys | Glu | Gly | Glu 70 | Cys | Ala |
| Phe | Pro | Leu 75 | Asp | Ser | Cys | Met | Asn 80 | Ala |
| Thr | Asn | His | Ala 85 | Ile | Leu | Gln | Ser | Leu 90 |
| Val | His | Leu | Met | Lys 95 | Pro | Asp | Val | Val |
| Pro 100 | Lys | Ala | Cys | Суѕ | Ala 105 | Pro | Thr | Lys |

| Leu | Ser 110 | Ala | Thr | Ser | Val | Leu 115 | Tyr | Tyr |
|-----|------------|------------|------------|-----|-----|------------|------------|------------|
| Asp | Ser | Ser 120 | Asn | Asn | Val | Ile | Leu 125 | Arg |
| Lys | His | Arg | Asn 130 | Met | Val | Val | Lys | Ala 135 |
| Cys | Gly | Cys | His. | | | | | |

11. The polypeptide chain of claim 8 wherein the amino acid sequence comprises (Sequence ID No. 3):

<u>hOP-2</u>

| Ala 1 | Val | Arg | Pro | Leu 5 | Arg | Arg | Arg | Gln |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Pro 10 | Lys | Lys | Ser | Asn | Glu 15 | Leu | Pro | Gln |
| Ala | Asn 20 | Arg | Leu | Pro | Gly | 11e 25 | Phe | Asp |
| Asp | Val | Asn 30 | Gly | Ser | His | Cly | Arg 35 | Gln |
| Val | Cys | Arg | Arg 40 | His | Glu | Lau | Tyr | Val 45 |
| Ser | Phe | Gln | Asp | Leu 50 | Gly | Trp | Leu | Asp |
| Trp 55 | Val | Ile | Ala | Pro | Gln 60 | Gly | Tyr | Ser |
| Ala | Tyr 65 | Tyr | Cys | Glu | Gly | Glu 70 | Cys | Ser |
| Phe | Pro | Leu 75 | Asp | Ser | Cys | Met | Asn 80 | Ala |
| Thr | Asn | His | Ala 85 | Ile | Leu | Gln | Ser | Leu 90 |

| Val | His | Leu | Met | Lys 95 | Pro | Asn | Ala | Val |
|------------|------------|------------|------------|-----------|------------|------------|------------|------------|
| Pro 100 | Lys | Ala | Cys | Cys | Ala 105 | Pro | Thr | Lys |
| Leu | Ser 110 | Ala | Thr | Ser | Val | Leu 115 | Tyr | Tyr |
| Asp | Glu | Ser 120 | Asn | Asn | Val | Ile | Leu 125 | Arg |
| Lys | Ala | Arg | Asn 130 | Met | Val | Val | Lys | Ala 135 |
| Cys | Gly | Cys | His. | | | | | |

12. The polypeptide chain of claim 8 wherein the amino acid sequence comprises (SEQ ID NO. 9):

hOP-2P

| | | | Pro 1 | Leu | Arg | Arg | Arg 5 | Gln |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Pro | Lys | Lys | Ser 10 | Asn | Glu | Leu | Pro | Gln 15 |
| Ala | Asn | Arg | Leu | Pro 20 | Gly | Ile | Phe | Asp |
| Asp 25 | Val | Asn | Gly | Ser | His 30 | Glγ | Arg | Gln |
| Val | Cys 35 | Arg | Arg | His | Glu | Lau 40 | Tyr | Val |
| Ser | Phe | Gln 45 | Asp | Leu | Gly | Trp | Leu 50 | Asp |
| Tyr | Val | Ile | Ala 55 | Pro | Gln | Gly | Tyr | Ser 60 |
| Ala | Tyr | Tyr | Cys | Glu 65 | Gly | Glu | Cys | Ser |

| Phe 70 | Pro | Leu | Asp | Ser | Cys 75 | Met | Asn | Ala |
|------------|------------|------------|------------|------------|------------|-------------------|-----------|------------|
| Thr | Asn 80 | His | Ala | Ile | Leu | Gln 85 | Ser | Leu |
| Val | His | Leu 90 | Met | Lys | Pro | Asn | Ala 95 | Val |
| Pro | Lys | Ala | Cys 100 | Cys | Ala | Pro | Thr | Lys 105 |
| Leu | Ser | Ala | Thr | Ser 110 | Val | Leu | Tyr | Tyr |
| Asp 115 | Glu | Ser | Asn | Asn | Val 120 | Ile | Leu | Arg |
| Lys | Ala 125 | Arg | Asn | Met | Val | Val 130 | Lys | Ala |
| Cys | Gly | Cys 135 | His. | | | | | |

13. The polypeptide chain of claim 8 wherein the amino acid sequence comprises (SEQ ID NO. 10):

hOP-2R

| | | | | | | Arg 1 | Arg | Gln |
|-----|----------|-----------|-----------|-----|-----|-----------|-----------|-----------|
| Pro | Lys 5 | Lys | Ser | Asn | Glu | Leu 10 | Pro | Gln |
| Ala | Asn | Arg 15 | Leu | Pro | Gly | Ile | Phe 20 | Asp |
| Asp | Val | Asn | Gly 25 | Ser | His | Gly | Arg | Gln 30 |
| Val | Cys | Arg | Arg | His | Glu | Leu | Tyr | Val |

| Ser 40 | Phe | Gln | Asp | Leu | Gly 45 | Ттр | Leu | Asp |
|------------|-----------|------------|------------|------------|-----------|------------|------------|------------|
| Tyr | Val 50 | Ile | Ala | Pro | Gln | Gly 55 | Tyr | Ser |
| Ala | Tyr | Tyr 60 | Cys | Glu | Gly | Glu | Cys 65 | Ser |
| Phe | Pro | Leu | Asp 70 | Ser | Cys | Met | Asn | Ala 75 |
| Thr | Asn | His | Ala | Ile 80 | Leu | Gln | Ser | Leu |
| Val 85 | His | Leu | Met | Lys | Pro 90 | Asn | Ala | Val |
| Pro | Lys 95 | Ala | Cys | Cys | Ala | Pro 100 | Thr | Lys |
| Leu | Ser | Ala 105 | Thr | Ser | Val | Leu | Tyr 110 | Tyr |
| Asp | Glu | Ser | Asn 115 | Asn | Val | Ile | Leu | Arg 120 |
| Lys | Ala | Arg | Asn | Met 125 | Val | Val | Lys | Ala |
| Cys 130 | Gly | Cys | His. | | | | | |

14. The polypeptide chain of claim 8 wherein the amino acid sequence comprises (SEQ ID NO. 11):

hOP-2S

Ser Gln Gln 1 Pro Phe Val Val Thr Phe Pt.e Arg Ala 5 10 Ser Pro Ser Pro Ile Arg Thr Pro Arg 15 20

| | Ala | Val | Arg | Pro 25 | Leu | Arg | A∴g | Arg | Gln 30 |
|---|------------|------------|------------|-------------|------------|------------|------------|------------|------------|
| | Pro | Lys | Lys | Ser | Asn 35 | Glu | Leu | Pro | Gln |
| | Ala 40 | Asn | Arg | Leu | Pro | Gly 45 | Ile | Phe | Asp |
| • | Asp | Val 50 | Asn | Gly | Ser | His | Gly 55 | Arg | Gln |
| - | Val | Cys | Arg 60 | Arg | His | Glu | Leu | Tyr 65 | Val |
| | Ser | Phe | Gln | Asp 70 | Leu | Gly | Trp | Leu | Asp 75 |
| • | Tyr | Val | Ile | Ala | Pro 80 | Gln | Gly | Tyr | Ser |
| • | Ala 85 | Tyr | Tyr | Cys | Glu | Gly 90 | Glu | Cys | Ser |
| | Phe | Pro 95 | Leu | Asp | Ser | Cys | Met 100 | Asn | Ala |
| | Thr | Asn | His 105 | Ala | Ile | Leu | GIn | Ser 110 | Leu |
| | Val | His | Leu | Met 115 | Lys | Pro | A.sn | Ala | Val 120 |
| | Pro | Lys | Ala | Cys | Cys 125 | Ala | Pro | Thr | Lys |
| | Leu 130 | Ser | Ala | Thr | Ser | Val 135 | Leu | Tyr | Tyr |
| | Asp | Glu 140 | Ser | Asn | Asn | Val | 11e 145 | Leu | Arg |
| | Lys | Ala | Arg 150 | Asn | Met | Val | Val | Lys 165 | Ala |
| | Cys | Gly | Cys | His. 170 | | | | | |

15. A polypeptide chain useful as a subunit of a dimeric osteogenic protein, said protein being capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix; said polypeptide chain having an amino acid sequence comprising (Sequence ID No. 2):

Prepro mOP-2

| | Met 1 | Ala | Met | Arg | Pro 5 | Gly | Pro | Leu |
|-----------|------------|-----------|-----------|-----------|-----------|------------|-----------|-----------|
| Trp | Leu 10 | Leu | Gly | Leu | Ala | Leu 15 | Cys | Ala |
| Leu | Gly | Gly 20 | Gly | His | Gly | Pro | Gly 25 | Pro |
| Pro | His | Thr | Cys 30 | Pro | Gln | Arg | Arg | Leu 35 |
| Gly | Ala | Arg | Asp | Arg 40 | Asp | Met | Gln | Arg |
| Glu 45 | Ile | Leu | Ala | Val | Leu 50 | Gly | Leu | Pro |
| Gly | Arg 55 | Pro | Asp | Pro | Val | His 50 | Asn | Pro |
| Pro | Leu | Pro 65 | Gly | Thr | Gln | Arg 70 | Ala | Pro |
| Leu | Phe | Met | Leu 70 | Asp | Leu | Tyr | His 80 | Ala |
| Met | Thr | Asp | Asp | Asp 85 | Asp | Cly | Gly | Pro |
| Pro 90 | Gln | Ala | His | Leu | Gly 95 | Arg | Ala | Asp |
| Leu | Val 100 | Met | Ser | Phe | Val | Asn 105 | Met | Val |

| • | Glu | Arg | Asp 110 | Arg | Thr | Leu | Gly | Tyr 115 | Gln |
|---|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Glu | Pro | His | Trp 120 | Lys | Glu | Phe | His | Phe 125 |
| | Asp | Leu | Thr | Gln | 11e 130 | Pro | Ala | Gly | Glu |
| _ | Ala 135 | Val | Thr | Ala | Ala | Glu 140 | Phe | Arg | Ile |
| • | Tyr | Lys 145 | Glu | Pro | Ser | Thr | His 150 | Pro | Leu |
| | Asn | Thr | Thr 155 | Leu | His | Ile | Ser | Met 160 | Phe |
| • | Glu | Val | Val | Gln 165 | Glu | His | Ser | Asn | Arg 170 |
| • | Glu | Ser | Asp | Leu | Phe 175 | Phe | Lėu | Asp | Leu |
| | Gln 180 | Thr | Leu | Arg | Ser | Gly 185 | Asp | Glu | Gly |
| | Trp | Leu 190 | Val | Leu | Asp | Ile | Thr 195 | Ala | Ala |
| | Ser | Asp | Arg 200 | Trp | Leu | Leu | Asn | His 205 | His |
| | Lys | Asp | Leu | Gly 210 | Leu | Arg | L¦≅u | Tyr | Val 215 |
| | Glu | Thr | Ala | Asp | Gly 220 | His | Ser | Met | Asp |
| | Pro 225 | Gly | Leu | Ala | Gly | Leu 230 | Leu | Gly | Arg |
| | Gln | Ala 235 | Pro | Arg | Ser | Arg | Gln 240 | Pro | Phe |
| | Met | Val | Thr 245 | Phe | Phe | Arg | Ala | Ser 250 | Gln |
| | Ser | Pro | Val | Arg 255 | Ala | Pro | Arg | Ala | Ala 260 |
| | | | | | | | | | |

| Arg | Pro | Leu | Lys | Arg 265 | Arg | Gln | Pro | Lys |
|------------|------------|------------|--------------------|------------|------------|------------|--------------------|------------|
| Lys 270 | Thr | Asn | Glu | Leu | Pro 275 | His | Pro | Asn |
| Lys | Leu 280 | Pro | Gly | Ile | Phe | Asp 285 | Asp | Gly |
| His | Gly | Ser 290 | Arg | Gly | Arg | Glu | V al 295 | Cys |
| Arg | Arg | His | Glu 300 | Leu | Tyr | Val | Arg | Phe 305 |
| Arg | Asp | Leu | Gly | Trp 310 | Leu | Asp | Trp | Val |
| Ile 315 | Ala | Pro | Gln | Gly | Tyr 320 | Ser | Ala | Tyr |
| Tyr | Cys 325 | Glu | Gly | Glu | Cys | Ala 330 | Phe | Pro |
| Leu | Asp | Ser 335 | Cys | Met | Asn | Ala | Thr 340 | Asn |
| His | Ala | Ile | Leu 345 | Gln | Ser | Leu | Val | His 350 |
| Leu | Met | Lys | Pro | Asp 355 | Val | Val | Pro | Lys |
| Ala 360 | Cys | Cys | Ala | Pro | Thr 365 | Lys | Leu | Ser |
| Ala | Thr 370 | Ser | Val | Leu | Tyr | Tyr 375 | Asp | Ser |
| Ser | Asn | Asn 380 | Val | Ile | Leu | Arg | Lys 385 | His |
| Arg | Asn | Met | V al 390 | Val | Lys | Ala | Cys | Gly 395 |
| Cys | His. | | | | | | | |

16. A polypeptide chain useful as a subunit of a dimeric osteogenic protein, sai's protein being

-91-

capable of inducing endochondral bone formation when implanted in a mammal in association with a matrix; said polypeptide chain comprising the amino acid sequence (Sequence ID No. 4):

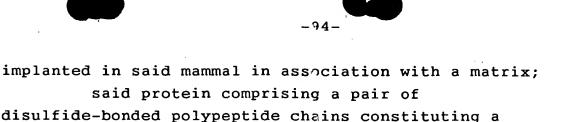
Prepro hOP-2

| Met 1 | Thr | Ala | Leu | Pro 5 | Gly | Pco | Leu | Trp |
|------------|------------|-----------|-----------|-----------|------------|------------|-----------|-----------|
| Leu 10 | Leu | Gly | Leu | Ala | Leu 15 | Cys | Ala | Leu |
| Gly | Gly 20 | Gly | Gly | Pro | Gly | Leu 25 | Arg | Pro |
| Pro | Pro | Gly 30 | Cys | Pro | Gln | A :g | Arg 35 | Leu |
| Gly | Ala | Arg | Asp 40 | Arg | Asp | Val | Gln | Arg 45 |
| Glu | Ile | Leu | Ala | Val | Leu | Gly | Leu | Pro |
| Gly 55 | Arg | Pro | Arg | Pro | Arg 60 | Ala | Pro | Pro |
| Ala | Ala 65 | Ser | Arg | Leu | Pro | Ala 70 | Ser | Ala |
| Pro | Leu | Phe 75 | Met | Leu | Asp | Leu | Tyr 80 | His |
| Arg | Met | Ala | Gly 85 | Asp | Asp | Asp | Glu | Asp 90 |
| Gly | Ala | Ala | Glu | Ala 95 | Leu | Gly | Arg | Ala |
| Asp 100 | Leu | Val | . Met | Ser | Phe 105 | Val | Asn | Met |
| Val | Glu 110 | Arg | Asp | Arg | Ala | Leu 115 | Gly | His |

| • | Gln | Glu | Pro 120 | His | Trp | Lys | Glu | Phe 125 | Arg |
|---|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| | Phe | Asp | Leu | Thr 130 | Gln | Ile | Pro | Ala | Gly 135 |
| | Glu | Ala | Val | Thr | Ala 140 | Ala | Glu | Phe | Arg |
| • | Ile 145 | Tyr | Lys | Val | Pro | Ser 150 | Ile | His | Leu |
| * | Leu | Asn 155 | Arg | Thr | Leu | His | Val 160 | Ser | Met |
| | Phe | Gln | Val 165 | Val | Gln | Glu | Gln | Ser 170 | Asn |
| | Arg | Glu | Ser | Asp 175 | Leu | Phe | Phe | Leu | Asp 180 |
| - | Leu | Gln | Thr | Leu | Arg 185 | Ala | Gly | Asp | Glu |
| | Gly 190 | Trp | Leu | Val | Leu | Asp 195 | Val | Thr | Ala |
| | Ala | Ser 200 | Asp | Cys | Trp | Leu | Leu 205 | Lys | Arg |
| | His | Lys | Asp 210 | Leu | Gly | Leu | Arg | Leu 215 | Tyr |
| | Val | Glu | Thr | Glu 220 | Asp | Gly | Fis | Ser | Val 225 |
| | Asp | Pro | Gly | Leu | Ala 230 | Gly | Leu | Leu | Gly |
| | Gln 235 | Arg | Ala | Pro | Arg | Ser 240 | Gln | Gln. | Pro |
| | Phe | Val 245 | Val | Thr | Phe | Phe | Arg 250 | Ala | Ser |
| | Pro | Ser | Pro 255 | Ile | Arg | Thr | Pro | Arg 260 | Ala |

| Val | Arg | Pro | Leu 265 | Arg | Arg | Arg | Gln | Pro 270 |
|------------|------------|------------|------------|------------|------------|-------------|------------|------------|
| Lys | Lys | Ser | Asn | Glu 275 | Leu | Pro | Gln | Ala |
| Asn 280 | Arg | Leu | Pro | Gly | Ile 285 | Phe | Asp | Asp |
| Val | His 290 | Gly | Ser | His | Gly | Arg 295 | Gln | Val |
| Cys | Arg | Arg 300 | His | Glu | Leu | Tyr | Val 305 | Ser |
| Phe | Gln | Asp | Leu 310 | Gly | Trp | Læu | Asp | Trp 315 |
| Val | Ile | Ala | Pro | Gln 320 | Gly | Tyr | Ser | Ala |
| Tyr 325 | Tyr | Cys | Glu | Gly | Glu 330 | Cys | Ser | Phe |
| Pro | Leu 335 | Asp | Ser | Cys | Met | A:sn 340 | Ala | Thr |
| Asn | His | Ala 345 | Ile | Leu | Gln | Ser | Leu 350 | Val |
| His | Leu | Met | Lys 355 | Pro | Asn | Ala | Val | Pro 360 |
| Lys | Ala | Cys | Cys | Ala 365 | Pro | Thr | Lys | Leu |
| Ser 370 | Ala | Thr | Ser | Val | Leu 375 | Tyr | Tyr | Asp |
| Ser | Ser 380 | Asn | Asn | Val | Ile | Leu 385 | Arg | Lys |
| Ala | Arg | Asn 390 | Met | Val | Val | I:ys | Ala 395 | Cys |
| Gly | Cys | His. | | | | | | |

17. A dimeric osteogenic protein capable of inducing endochondral bone formation in a mammal when



18. The polypeptide chain of claim 1, 6, 8, 15 or 16 produced by expression of recombinant DNA in a host cell.

dimeric species, wherein each said polypeptide chain is the polypeptide chain of claim 1, 6, 8, 15 or 16.

- 19. The polypeptide chain of claim 15 wherein said host cell is a procaryotic host cell.
- 20. The polypeptide chain of claim 15 wherein said host cell is a mammalian cell.
- 21. The polypeptide of claim 1, 6, 8, 15 or 16 that is glycosylated.
- 22. A DNA encoding the polypeptide chain of claim 1, 6, 8, 15 or 16.
- 23. A dimeric protein comprising a pair of polypeptide chains expressed from a DNA sequence sufficiently duplicative of the sequence of Sequence ID No. 2 or Sequence ID No. 4 such that, when said polypeptide chains are oxidized to produce a disulfide-bonded dimeric species, the dimeric species has a conformation that is capable of inducing endochondral bone or cartilage formation when disposed within a matrix and implanted in a mammal.